February 13, 2007

Mr. John Morris
American Chemistry Council
Aliphatic Esters Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Morris:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Sorbitan Esters Category posted on the ChemRTK HPV Challenge Program Web site on January 22, 2004. I commend the Aliphatic Esters Panel for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: C. Augustyniak
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Sorbitan Esters Category

Summary Of EPA Comments

The sponsor, the American Chemistry Council's Aliphatic Esters Panel, submitted a revised test plan and robust summaries for the Sorbitan Esters Category, dated November 26, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 22, 2004. The category consists of 6 substances. Robust summaries for one proposed structural analog, sorbitan tetraester with C6-C10 fatty acids (CAS No. 228573-47-5), were also submitted.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The category definition is clear.

2. Category Justification. Similarities in chemical structure and trends in physicochemical and environmental fate values as well as data for most mammalian toxicity endpoints support the category.

3. Analog Justification. The submitter proposed one structural analog, a mixture of sorbitan tetraesters with total carbon numbers ranging from C30 to C46, with little justification. Although the analog could be reasonable for health effects, the submitter needs to provide a rationale that describes why the analog will behave like the category members. For the ecotoxicity endpoints, the analog is not appropriate to represent the range of this category.

4. Physicochemical Properties. The submitter needs to provide measured melting points for these chemicals, measured water solubility data for some members, and robust summaries for each endpoint for the sponsored substances.

5. Environmental Fate. The submitter needs to confirm the hydrolysis values for sorbitan monooleate, sorbitan sesquioleate, and sorbitan trioleate. The submitter needs to provide robust summaries for the photodegradation, stability in water, and fugacity endpoints.

6. Health Effects. EPA reserves judgement on the genetic toxicity (gene mutations) endpoint until critical study elements are submitted and on the genetic toxicity (chromosomal aberrations) endpoint pending a stronger analog justification. The submitter needs to address deficiencies in the robust summaries.

7. Ecological Effects. The submitted data are inadequate to satisfy the acute toxicity to fish, aquatic invertebrates, and algae endpoints for the category. Data for sorbitan esters are needed for several points along the molecular size/weight/solubility range to characterize the aquatic toxicity of the category because of the wide variation in estimated water solubility and log K_{ow}. In addition, testing of chronic toxicity to invertebrates is needed for an appropriate category member.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments On The Sorbitan Esters Category Challenge Submission

Category Definition

The category consists of six members that are mono-, di-, and triesters ranging in carbon number from C18 to C60. Sorbitan monolaurate (CAS No. 1338-39-2), sorbitan monostearate (CAS No. 1338-41-6), sorbitan monooleate (CAS No. 1338-43-8), and sorbitan trioleate (CAS No. 26266-58-0) are single substances. Sorbitan sesquioleate (CAS No. 8007-43-0) is a mixture of sorbitan mono- and dioleate,

while sorbitan, monoesters with coco fatty acids (CAS No. 68154-36-9) combines sorbitan monoesters of predominantly C12 and C14 fatty acids.

Table 1B and Figure 2 of the test plan show 228753-47-5 as the CAS No. for sorbitan, fatty acids C6-10, tetraester. The correct CAS No. for this substance is 228573-47-5.

Category Justification

The submitter bases the grouping of the sponsored and analog sorbitan esters on structural and chemical similarities and the expected trends in physicochemical, environmental fate and toxicological properties, reflecting the differing number and length of their long-chain fatty ester functions,

Acute oral toxicity data support the category. While data for the mutagenicity endpoint need further support, the consistently negative available data support the grouping. Similarly, available data for repeated-dose and reproductive/developmental toxicity endpoints indicate toxicity at high doses only.

The category appears adequate for ecotoxicity on the basis of structure and property trends.

Analog Justification

The proposed sorbitan tetraester analog has no free hydroxyl groups, unlike the sponsored substances, which each have one to three nonesterified hydroxyl groups. The submitter needs to describe why this substance will behave similarly to the category members. For ecotoxicity, the proposed analog is not appropriate to represent the full range of this category. The wide range of estimated water solubility and log K_{ow} values suggests that data for sorbitan esters at several points of the size/molecular weight/ solubility range are needed to characterize the anticipated range of aquatic toxicity.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for boiling point, vapor pressure, and octanol/water partition coefficient are adequate for the purposes of the HPV Challenge Program. However, these data need to be provided in robust summary format. For the purposes of the HPV Challenge Program, the submitter needs to provide robust summaries for each endpoint for each of the category members. It is not sufficient to provide data only in the test plan.

Melting point. The submitter provided estimated melting point values above 0 ^{o}C for all chemicals in this category. Estimated values above 0 ^{o}C are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured values for these chemicals following OECD guidelines. Data from published sources are adequate, as long as the submitter identifies the source(s).

Water solubility. The data provided by the submitter for sorbitan sesquioleate and trioleate are adequate because their estimated values are below 1 µg/L. Values above this limit need to be measured. The values for the other four members are above 1 µg/L. Because these chemicals are surfactants, it may be difficult to provide meaningful water solubility data for them. Instead, the submitter needs to provide measured dispersibility values for these four chemicals (see “Dispersions and emulsions” in *Guidance on Aquatic Toxicity Testing of Difficult Substances and Mixtures* at http://www.olis.oecd.org/olis/2000doc.nsf/LinkTo/env-jm-mono(2000)6). This information is needed in order to perform meaningful aquatic toxicity testing.

Environmental Fate (photodegradation, stability in water, biodegradation and fugacity)

The data provided by the submitter for photodegradation, biodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. However, all data need to be provided in robust summary format, including the inputs used to run the level III fugacity model.

Stability in water. The submitter needs to confirm the calculated hydrolysis half-life values for sorbitan monooleate (2.2 years), sorbitan sesquioleate (0.9 years) and sorbitan trioleate (0.59 years). EPA calculated (EPIWIN v. 3.12) a value of 1.5 years for sorbitan trioleate. EPA also calculated values for the components of sorbitan sesquioleate: sorbitan dioleate (1.8 years) and monooleate (7.7 years).

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are provided for the acute and reproductive toxicity endpoints for the category. Data provided for repeated-dose and developmental toxicity endpoints only characterize the higher carbon chain-length range of the category. However, these data suggest that further testing would not provide any useful new information, because the esters are expected to metabolize to sorbitan and the corresponding common fatty acids, which are readily metabolized in mammalian systems to excretable metabolites. Therefore, no further testing is necessary for these endpoints for the purposes of the HPV Challenge Program.

Genetic Toxicity (Gene Mutations). EPA reserves judgement on the genetic toxicity (gene mutations) endpoint until critical data elements are submitted (see Specific Comments on the Robust Summaries).

Genetic Toxicity (Chromosomal aberrations). EPA reserves judgement on the genetic toxicity (chromosomal aberrations) endpoint pending the receipt of a stronger analog justification. The test plan stated that sorbitan monostearate "did not cause any chromosomal aberrations in the Syrian golden hamster embryo cell assay and did not show clastogenic activity." However, this study does not address the chromosomal aberrations endpoint because the cell transformation assay does not necessarily measure clastogenesis. The submitter needs to support the analog justification with data or provide data for this endpoint according to OECD TG 473.

Ecological Effects (fish, invertebrates, and algae)

The submitted data are inadequate to satisfy the acute toxicity endpoints for fish, aquatic invertebrates, and algae. Data for sorbitan esters at both the upper and lower ends and one from the mid-point of the size/molecular weight range are needed for characterizing the aquatic toxicity of the category because of the wide variation in estimated water solubility and log K_{ow}: water solubility estimates range from 13 mg/L to 6 x 10^{-19} mg/L and log K_{ow} estimates range from 3 to 21. The selection of test substances should be based on the water solubility (dispersibility) tests because of the low water solubility/dispersibility values of these chemicals.

No data were provided to characterize chronic toxicity of category members to invertebrates. However, physicochemical properties indicate that some category members will persist in the environment with the potential to bioaccumulate. Therefore, EPA recommends chronic toxicity testing (see below).

Fish. Data are inadequate to satisfy the endpoint. Data from 96-hour acute fish toxicity studies on C18 (sorbitan monolaurate) and C24 (sorbitan monooleate) category members are inadequate because the estimated (EPIWIN) water solubilities of the two category members (13 and 0.02 mg/L, respectively) are less than the maximum concentrations tested (100 and 1000 mg/L, respectively).

Invertebrates and Algae. No data were available for any of the category members. Tests for sorbitan esters at the upper and lower ends and one in the mid-range of the size/molecular weight/solubility range are needed to characterize the aquatic toxicity of the category.

Chronic Toxicity to Invertebrates. Because some of the category members have the potential to persist in the environment and to bioaccumulate, EPA recommends a chronic toxicity study in aquatic invertebrates for a category member having an estimated log K_{ow} value in the range 5-8.

Specific Comments on the Robust Summaries

Health Effects

General. Test substance purity needs to be stated for all studies where available.

Repeated-Dose Toxicity. The 80-week oral feeding study of sorbitan monostearate in mice needs to include the hematology and clinical chemistry parameters examined. The two year feeding study summary should include, if available, the list of organs weighed and tissues examined histologically at necropsy.

Genetic Toxicity (Gene Mutations). All study summaries need to describe the criteria for negative and positive responses observed, to allow the evaluation of data. For the sorbitan tetraester analog the mean number of revertent colonies per plate, replicates per concentration, culture conditions and statistical methods used need to be included in the robust summaries. Only two strains of bacteria were tested in the study submitted for sorbitan monostearate whereas current guidelines recommend the testing of 5 strains. The concentrations tested were well below the guideline recommendations of 5000 μg/plate. The submitter needs to include the rationale for the testing concentrations and indicate if any cytotoxicity was observed. Missing study information included the positive and negative control responses, number of revertent colonies per plate, replicates per concentration, culture conditions and statistical methods used.

Genetic Toxicity (*Chromosomal aberrations).* The study using the sorbitan tetraester lacked information on incubation conditions and evidence of testing up to the limit concentration or to significant cytotoxicity.

Reproductive Toxicity. Details missing from the robust summary of a two-year, four-generation reproductive and developmental toxicity feeding study of sorbitan monostearate in rats included the specific testing guideline, statistical methods used, and the results of statistical analyses.

Five additional robust summaries submitted as dietary combined repeated-dose/reproductive toxicity studies on two samples of sorbitan monooleate, one sample of sorbitan monolaurate and two samples of sorbitan monostearate were missing study details including test substance purity, specific details of gross necropsy, histopathological examination, and weighing of the reproductive organs. As these studies are needed to assess the overall adequacy of data for this endpoint for the category, the submitter needs to provide separate reproductive toxicity summaries for these studies that present the relevant reproductive organ data (gross abnormalities, relative organ weights, and histopathology findings).

A robust summary submitted for a 28-day repeated-dose oral gavage toxicity study of the sorbitan tetraester in rats was missing study details including gross necropsy findings and histopathological examination of the reproductive organs and tissues.

Developmental Toxicity. If available, the following study results should be included in the robust summary submitted for a two-year, four-generation reproductive and developmental toxicity feeding study in rats on sorbitan monostearate: pup weight on days 0 or 1 postpartum, pup sex, postimplantation loss, abnormal pup behavior and external examination of pups for gross abnormalities and statistical methods used.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.